A Study of Adjuvant Chemoradiotherapy with Tri-weekly Cisplatin for Postoperative High-risk Oral Squamous Cell Carcinoma

Mitsunobu OTSURU[*1], Yoshihide OTA[*1], Takayuki AOKI[*1], Masashi SASAKI[*1], Takatugu SUZUKI[*1], Yuya DENDA[*1], Miho TAKAHASHI[*1], Takeshi AKIBA[*2] and Akihiro KANEKO[*1]

[*1]*Department of Oral and Maxillofacial Surgery, Division of Surgery, Tokai University School of Medicine*
[*2]*Department of Radiology, Division of Surgery, Tokai University School of Medicine*

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Objective: The aim of this study was to assess the feasibility and safety profile of concurrent chemoradiotherapy with cisplatin in Japanese patients with postoperative high-risk oral cancer.
Methods: Patients with high-risk pathological features were selected from patients with oral squamous cell carcinoma who underwent surgery at the Department of Oral and Maxillofacial Surgery, Tokai University Hospital. Patients were given adjuvant chemoradiotherapy with tri-weekly cisplatin (100 mg/m2) (66 Gy/33 Fr), and the treatment completion rate was examined.
Results: A total of 27 patients were enrolled between April 2011 and December 2012, including 19 males and 8 females. The median follow-up period was 36 months, and the protocol completion rate was 81.5%. Grade 3 or higher adverse events included leukopenia in 16 patients (59.3%), anemia in 7 patients (25.9%), mucositis in 2 patients (7.4%), increased creatinine in 1 patient (3.7%), nausea in 4 patients (14.8%), and anorexia in 12 patients (44.4%). The 3-year overall survival rate was 66.7%, relapse-free survival rate was 63.0%, and locoregional control rate was 77.8%.
Conclusion: The feasibility and safety profile of concurrent chemoradiotherapy with cisplatin in Japanese patients with postoperative high-risk oral cancer were comparable to pivotal phase III trials.

Key words: oral cancer, standard treatment, adjuvant chemoradiotherapy, cisplatin

INTRODUCTION

At present, the treatment for head and neck cancer follows the standard treatment guidelines provided by the National Comprehensive Cancer Network (NCCN) [1]. These guidelines recommend performing a radical excision for the treatment of resectable oral squamous cell carcinoma (OSCC) and postoperative concurrent chemoradiotherapy for high-risk patients [1]. According to the protocol, patients are administered tri-weekly cisplatin 100 mg/m2 in three cycles concurrent to a postoperative chemoradiotherapy with 66 Gy. However, this treatment approach remains questionable as to whether it is applicable in Japan, considering the physical constructional differences between Westerners and Japanese. Therefore, a feasibility study of concurrent postoperative chemoradiotherapy with cisplatin was conducted in head and neck cancer primarily at the National Cancer Center Hospital East [2]. The treatment completion rate was 80%, and it was considered that this was not always impossible. However, due to a difference observed in radiosensitivity and survival rate between OSCC and other head and neck cancers, it is necessary to review the feasibility and therapeutic effects only on oral cancer. We therefore investigated the feasibility of concurrent postoperative chemoradiotherapy with cisplatin in Japanese patients with postoperative high-risk OSCC according to the NCCN guidelines.

PATIENTS AND METHODS

Patients

This study included 27 patients with high-risk pathological features selected from OSCC patients who underwent surgery at the Department of Oral and Maxillofacial Surgery, Tokai University Hospital, between April 2011 and December 2012. The high-risk features included multiple lymph node metastasis, extracapsular spread, and microscopically involved mucosal margins of resection according to the postoperative histopathological diagnosis.

The following inclusion criteria for treatment were also established: 1) oral cancer whose primary lesion was diagnosed histopathologically as squamous cell carcinoma; 2) age range between 20 and 75 years; 3) ECOG Eastern Cooperative Oncology Group Performance Status (PS): 0 or 1; 4) no previous treatment history of radiation therapy (RT)/chemotherapy/hormone treatment, including other cancers; and 5) blood test showing neutrophil count ≥ 1500 mm3; platelet count ≥ 10×10^4 mm3; and creatinine clearance (CCr) ≥ 60 mL/min.

Blood chemistry, complete blood cell count, chest X-ray, computed tomography and/or magnetic resonance imaging of head and neck area, and thoracoabdominal computed tomography were performed

Mitsunobu OTSURU, Department of Oral and Maxillofacial Surgery, Division of Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan Tel: +81-463-93-1121 Fax: +81-463-91-5902 E-mail:ootsuru@is.icc.u-tokai.ac.jp

Table 1 Patient characteristics (n = 27)

		Number of patients
Age	Median(range)	68(35-75)
	Male / Female	19 /8
Performance Status	0	27
Primary site	Tongue	13
	Mandible	5
	Maxilla	4
	Buccal mucosa	3
	Hard palate	1
	Intraosseous of jaw	1
Stage	Ⅲ	1
	ⅣA	10
	ⅣB	8
	Locoregional recurrent disease	8
Histology	Well differentiated	15
	Moderately differentiated	11
	Poorly differentiated	1
High-risk features	Extracapsular spread	16
	Multiple lymph node metastasis	14
	Microscopically involved mucosal margins of resection	6

preoperatively for all patients.

Treatment

The RT regimen consisted of a prescribed dose of 66 Gy/33 Fr administered at 2 Gy per once-daily fraction using a Linac. The whole neck area (including primary lesions for patients with positive microscopic resection margins) was irradiated with a dose of 60 Gy and a boost of 6 Gy/3 Fr. The chemotherapy regimen consisted of three cycles of cisplatin at 100 mg/m2 tri-weekly (days 1, 22, and 43). Sufficient hydration was performed before and after the administration of cisplatin.

If Grade 3 or higher hematological toxicity occurred, the dose of cisplatin was reduced to 80 mg/m2. If the hematological toxicity persisted, the administration of cisplatin was discontinued. This treatment was initiated within 56 days after the radical surgical procedure. The treatment completion rate is the proportion of patients receiving RT of ≥ 60 Gy and chemotherapy of cisplatin being ≥ 200 mg/m2 within 14 days after RT.

Study design

Patients were enrolled postoperatively and assigned to receive adjuvant concurrent chemoradiotherapy with cisplatin. Consistent with the intention-to-treat principle, all patients were included in all statistical analyses. The primary endpoint was the treatment completion rate. The secondary endpoints were overall survival (OS), relapse-free survival (RFS), locoregional control rate (LCR), and an adverse event. The survival curves were estimated using Kaplan-Meier methods, and comparisons between the survival curves were performed using the log-lank test. Treatment-related adverse events were scored according to the Common Toxicity Criteria of the National Cancer Institute (CTCAE), version 4.0, and categorized as acute (occurring within 90 days after the initiation of chemoradiotherapy) or late (continuing or occurring after 90 days).

Univariate analysis for survival was performed on gender, primary site (tongue or other), disease status (locally advanced disease or locoregional recurrent disease), tumor differentiation, and cumulative cisplatin dose.

All analyses were conducted using the Windows version of SPSS version 23 (Japan IBM, Tokyo, Japan).

This study approved by committee of the institutional review board for clinical research at Tokai University School of Medicine (12R-064).

RESULTS

Between April 2011 and December 2012, 27 patients with OSCC were enrolled, including 19 males and 8 females, with an age range of 35–75 years (median age: 68 years) (Table 1).

The performance status was zero for all patients and they received no prior chemotherapy. The primary sites included tongue in 13 patients, lower gingiva in 5 patients, upper gingiva in 4 patients, buccal mucosa in 3 patients, palate in 1 patient, and intraosseous of jaw in 1 patient. The high-risk features included extracapsular spread of lymph node metastasis in 16 patients, positive microscopic resection margins in 14 patients, and multiple lymph node metastases in 6 patients. Stage III was observed in 1 patient, Stage IV-A in 10 patients, Stage IV-B in 8 patients, and locoregional recurrent disease in 8 patients. Histology included well-differentiated tumors in 15 patients, moderately differentiated tumors in 11 patients, and poorly differentiated tumors in 1 patient. Treatment was started 14–47 days postoperatively (mean: 31.3 days). Among the 27 patients, 22 (81.5%) completed the treatment of concurrent postoperative chemoradiotherapy with cisplatin. Reasons for discontinuation included hematological toxicity in 3 patients, patient's refusal of treatment in 1 patient, and insufficient irradiation dose in 1 patient. In addition, 16 (59.3%) of the 27 patients received three cycles of chemotherapy. Cisplatin dose was reduced in 17 patients due to hematological toxicity. The median follow-up period was 36 months.

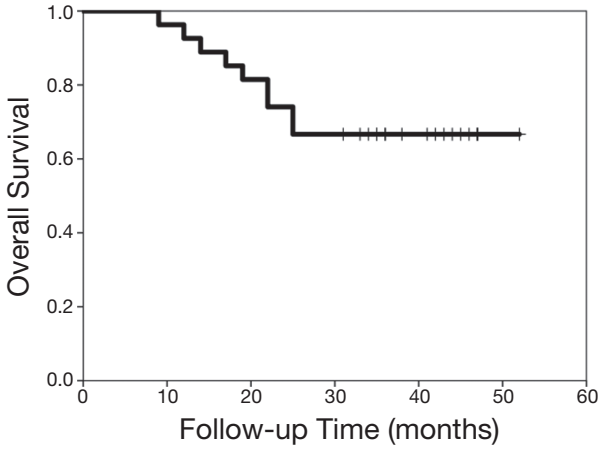

Fig. 1 Kaplan-Meier estimates of overall survival (n = 27).

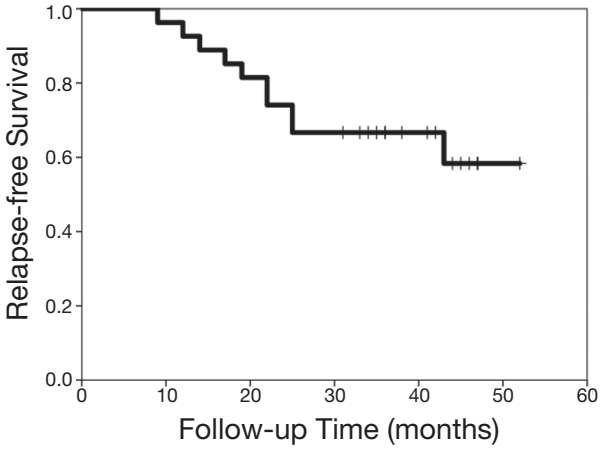

Fig. 2 Kaplan-Meier estimates of relapse-free survival (n = 27).

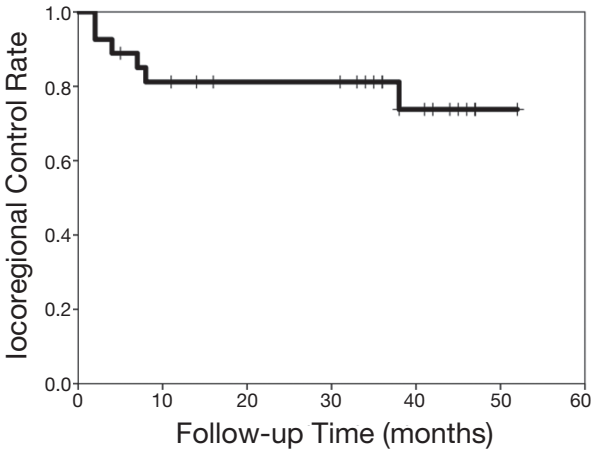

Fig. 3 Kaplan-Meier estimates of locoregional control rate (n = 27).

The 3-year OS was 66.7%, RFS was 63.0%, and LCR was 77.8%. The causes of death included locoregional recurrence in 2 patients, neck recurrence in 1 patient, distant metastasis in 4 patients, and neck recurrence + distant metastasis in 2 patients (Fig. 1–3). Based on the mortality by high-risk features, patients with multiple lymph node metastasis and extracapsular spread had a poor prognosis (Fig. 4). The distant metastasis rate was 22.2%. According to the CTCAE version 4.0, Grade 3 or higher adverse events included leukopenia in 16 patients (59.3%), anemia in 7 patients (25.9%), mucositis in 2 patients (7.4%),

febrile neutropenia in 1 patient (3.7%), increased creatinine in 1 patient (3.7%), nausea in 4 patients (14.8%), and anorexia in 12 patients (44.4%).

Grade 1 mucositis was observed in 16 patients and Grade 2 in 6 patients. Grade 1 dermatitis was observed in 20 patients and Grade 2 in 6 patients (Table 2).

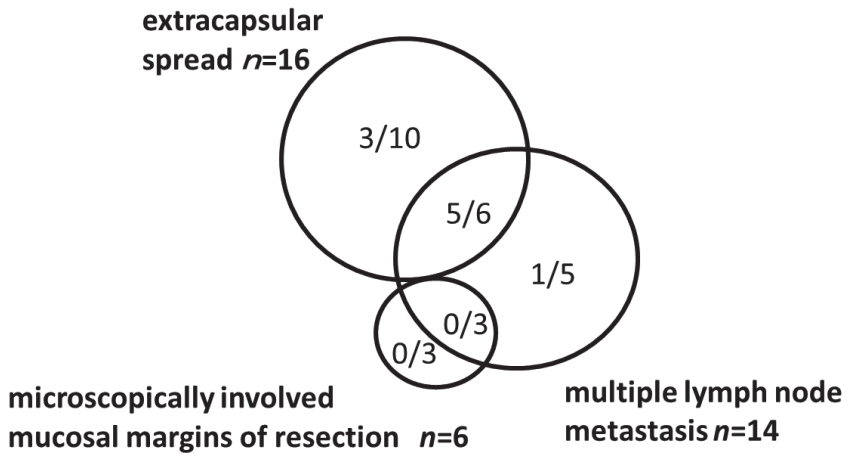

Fig. 4 Overall survival failure by high-risk feature (n = 27).

Table 2 Adverse events (n = 27)

Adverse events	Number of patients				
	Grade1	Grade2	Grade3	Grade4	%Grade3/4
Leucopenia	2	9	16	0	59.3
Neutropenia	13	7	7	0	25.9
Anemia	5	7	7	0	25.9
Thrombocytopenia	2	1	1	0	3.7
Nausea	6	8	4	0	14.8
Anorexia	8	4	12	0	44.4
Mucositis	16	6	2	0	7.4
Dermatitis	20	6	0	0	0
Creatinine	11	2	1	0	3.7
Febrile Neutropenia	0	0	1	0	3.7

Regarding late adverse events, Grade 2 osteonecrosis was observed in 7 patients (25.9%) (Table 3). Univariate analysis for LCR, RFS, and OS showed no significant contributor to survival (Table 4).

DISCUSSION

In the EORTC99231 and RTOG9501 studies, chemoradiotherapy was not used as a monotherapy for oral cancer; hence, it is necessary to verify if it is really beneficial for oral cancer [3, 4]. Furthermore, there are few reports on the use of concurrent postoperative chemoradiotherapy with cisplatin in Japanese patients [2, 5]. Therefore, we conducted a clinical study to examine the feasibility of postoperative chemoradiotherapy as standard treatment in Japanese patients with oral cancer.

The rate of completing at least two cycles of cisplatin in treatment with tri-weekly cisplatin plus RT is 79–93%, while it is 100% in the phase II study in Japanese patients [3–8]. Furthermore, in the feasibility study of tri-weekly cisplatin plus RT conducted at the National Cancer Institute, 20 of 25 patients completed treatment, with a treatment completion rate of 80% [2]. The treatment completion rate was 81.5% in this study, which is consistent with the feasibility study, and there were no issues with tolerability of this treatment in Japanese patients.

In this study, sufficient hydration before treatment was able to minimize cisplatin-induced renal impairment. Furthermore, mucositis occurrence was mild. This was considered to be due to the fact that in this study, radiation field does not include primary lesions in patients other than those with positive microscopic resection margins, and several patients with positive microscopic resection margins had carcinoma of upper gingiva and mucositis was unlikely to occur considering the radiation field. Regarding whether the radiation field should include primary lesions, radiation was given to the area of the lesions in both the RTOG9501 [3] and EORTC22931 [4] studies. However, no primary lesion was confirmed in patients other than those with positive microscopic resection margins in this study. For OSCC, radiotherapy of primary lesions in patients

Table 3 Late adverse events (n = 27)

Adverse events	Number of patients				
	Grade1	Grade2	Grade3	Grade4	%Grade3/4
Leucopenia	3	2	0	0	0
Neutropenia	0	1	0	0	0
Anemia	1	2	0	0	0
Thrombocytopenia	2	0	1	0	3.7
Nausea	0	0	0	0	0
Anorexia	0	0	0	0	0
Mucositis	0	0	0	0	0
Dermatitis	0	0	0	0	0
Creatinine	2	1	0	0	0
Osteonecrosis	0	3	0	0	0

Table 4 Univariate analysis for survival (n = 27)

	Number of patients	Three-year locoregional control rate(%)	*p*-value	Three-year RFS(%)	*p*-value	Three-year OS(%)	*p*-value
Gender							
Female	19	78.9	0.995	63.2	0.784	63.2	0.498
Male	8	75		62.5		75	
Site of primary tumor							
Tongue	13	84.6	0.576	69.2	0.69	69.2	0.909
Other	14	71.4		57.1		64.3	
Disease status							
Locally advanced disease	19	68.4	0.105	57.9	0.392	63.2	0.603
Locoregional recurrent disease	8	100		75		75	
Tumor differentiated							
Well differentiated	15	80	0.649	66.7	0.544	73.3	0.37
Moderately or poorly differentiated	12	75		58.3		58.3	
Cumulative cisplatin dose							
≧200mg/㎡	23	73.9	0.271	60.9	0.517	65.2	0.725
<200mg/㎡	4	100		75		75	
Treatment completion							
Yes	22	77.3	0.767	63.6	0.835	63.6	0.515
No	5	80		60		80	

other than those with positive microscopic resection margins was considered unnecessary. Decreased white blood cell count was observed in 16 patients (59.3%) and the hematological toxicity was higher than that in other studies (EORTC22931: 13%; RTOG9501: 38%; Kiyota *et al.*: 48%); however, the grade level was 3 for all patients and the event could be treated with appropriate dose reduction [2–4].

In this study, late adverse events such as osteonecrosis were observed in 3 patients (11.1%). A marked reduction in the quality of life was observed in patients with osteonecrosis. In the case of oral cancer, the mandible was considered more likely to be exposed to radiation compared with other regions, thus causing osteonecrosis. It was therefore deemed necessary to introduce the intensity-modulated RT (IMRT) with regard to RT.

The 3-year OS, RFS, and LCR in this study were 66.7%, 63.0%, and 77.8%, respectively. The 5-year OS, RFS, and LCR in the RTOG9501 [3] and EORTC22931 [7] studies were reported to be 49%, 40%, and 81% and 53%, 47%, and 79%, respectively. Kiyota *et al.* reported that the 3-year OS, RFS, and LCR were 60%, 43%, and 73%, respectively [2]. Although a simple comparison may be difficult due to different background and short duration of follow-up of the respective studies, treatment outcome in this study was considered appropriate. However, the report by Kiyota *et al.* showed no significant difference, but OS has a tendency to be worsened in the oral region as compared to other regions (58.8% vs 75.0%, P = 0.055) [2]. Furthermore, Yanagimoto *et al.* reported that a multicenter analysis of oral cancer with metastasis-positive lymph nodes showed no significant

difference in the survival rates between postoperative chemoradiotherapy and radiation monotherapy [9]. Furthermore, reduction in patient's quality of life was also significant for treatment-induced osteonecrosis. Accordingly, it was considered necessary to re-examine the clinical benefit of concurrent chemoradiotherapy with cisplatin in patients with oral cancer in large-scale studies. In addition, the rate of distant metastases in this study was 22.2%, which was almost comparable to that in the RTOG9501 [3] and EORTC99231 [4] studies. The LCR improved, but the rate of distant metastases worsened. Since concurrent chemoradiotherapy with cisplatin is focused on local therapy, it is necessary to shift the target to the treatment for distant metastases.

Cisplatin has a radiosensitizing effect and is a key drug for head and neck cancer. If > 200 mg/m2 of cisplatin in total is given concurrently with RT, an additive effect of RT can be expected [10]. Therefore, a certain therapeutic effect can be secured with a total cisplatin dose of ≥200 mg/m2, and thus the treatment was completed with a cisplatin dose of ≥200 mg/m2 in this study.

However, this study showed no significant difference between cisplatin doses of > 200 mg/m2 and < 200 mg/m2. In 2012, Kiyota *et al*. [2] reported that cisplatin dose of ≥ 240mg/m2 for oral cancer is a significant prognostic factor. Hence, further investigation on the total dose of cisplatin is required in the future.

In this study, poor prognostic factors, as previously pointed out, including extracapsular spread of lymph node metastasis [11–13], positive microscopic resection margins [11–13], and multiple lymph node metastases [11–12, 14–15], were considered as high-risk features. In the pooled analysis of RTOG9501 and EORTC22931 studies, extracapsular spread of lymph node metastasis and positive microscopic resection margins were significant high-risk features. However, there was no factor for multiple lymph node metastases in the EORTC22931 analysis, and its significance has not been demonstrated [13]. However, there are several reports that three or more lymph node metastases or metastases extending into two regions are considered as poor prognosis and multiple lymph node metastases are often discussed [16]. In addition, as the primary endpoint is treatment completion rate in this study, multiple lymph node metastases were included in the high-risk group. Therefore, most of the patients who died specifically had extracapsular spread of lymph node metastasis + multiple lymph node metastases. Multiple lymph node metastases are prognostic factors that should be adequately considered.

CONCLUSIONS

The feasibility and safety profile of concurrent chemoradiotherapy with cisplatin in Japanese patients with postoperative high-risk oral cancer were comparable to pivotal phase III trials.

CONFLICT OF INTEREST STATEMENT

None declared.

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